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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CORCEPT THERAPEUTICS, INC., **Plaintiff,** **v.** **TEVA PHARMACEUTICALS USA, INC.,** **Defendant.**	Civil Action No. 18-3632 (SDW)(LDW) (consolidated) [redacted] Hon. Susan D. Wigenton, U.S.D.J. Hon. Leda D. Wettre, U.S.M.J. (Filed Electronically)

MEMORANDUM OF LAW IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF U.S. PATENT NO. 10,195,214

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TABLE OF EXHIBITS

Short Citation*	Full Citation	Exhibit Number
SMF	Local Civil Rule 56.1 Statement of Undisputed Material Fact	
'214 Patent	U.S. Patent No. 10,195,214	A
2012 Korlym® Label	2012 Korlym® Full Prescribing Information (CORMIFE-T-00002807-29)	B
2019 Korlym® Label	2019 Korlym® Full Prescribing Information (CORMIFE-T-00062787-809)	C
CDC	"Treatment for Aspergillosis," Centers for Disease Control and Prevention (Jan. 8, 2021), https://www.cdc.gov/fungal/diseases/aspergillosis/treatment.html	D
Charmandari	E. Charmandari et al., "Adrenal insufficiency," *Lancet*, 383(9935):2152-67 (2014) (CORMIFE-T-00011065-80)	E
Cuevas-Ramos	D. Cuevas-Ramos et al., "Update on medical treatment for Cushing's disease," *Clin. Diabetes & Endocrinol.*, 2:16 (2016) (TEVA_MIFE-0071171-83)	F
Dang	C.N Dang, et al., "Pharmacological Management of Cushing's Syndrome: An Update," *Arq. Bras. Endocrinol. Metab.*, 51(8):1339-1348 (2007) (TEVA_MIFE-0071205-214)	G
DeRosa Tr.	Gregg DeRosa Deposition Transcript (July 2, 2020)	H
FDA Approval Letter	Korlym® FDA Approval Letter (CORMIFE-T-00068874-80)	I
February Letter	February 18, 2021 Letter from Teva to the Honorable Leda D. Wettre, U.S.M.J.	J

Short Citation*	Full Citation	Exhibit Number
Fleseriu 2012	M. Fleseriu et al., "Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome," *J. Clin. Endocrinol. Metab.*, 97(6):2039-49 (2012) (TEVA_MIFE-0071355-65)	K
Fleseriu 2013(a)	M. Fleseriu & S. Petersenn, "New avenues in the medical treatment of Cushing's disease: corticotroph tumor targeted therapy," *J. Neurooncol.*, 114:1-11 (2013) (TEVA_MIFE-0071376-86)	L
Fleseriu 2013(b)	M. Fleseriu et al., "A New Therapeutic Approach in the Medical Treatment of Cushing's Syndrome: Glucocorticoid Receptor Blockade with Mifepristone," *Endocrine Practice*, 19(2):313-26 (2013) (TEVA_MIFE-0071387-400)	M
Guelho	D. Guelho & A.B. Grossman, "Emerging drugs for Cushing's disease," *Expert Opin. Emerging Drugs*, 20(3):463-78 (2015) (TEVA_MIFE-0071474-90)	N
Itraconazole Label	Sporanox® (Itraconazole) Full Prescribing Information (CORMIFE-T-00010651-721)	O
Mayo Clinic	"Hyperglycemia in Diabetes," The Mayo Clinic (Nov. 3, 2018), https://www.mayoclinic.org/diseases-conditions/hyperglycemia/ symptoms-causes/syc-20373631	P
Morgan	F.H. Morgan & M.J. Laufgraben, "Mifepristone for Management of Cushing's Syndrome," *Pharmacotherapy*, 33(3):319-29 (2013) (TEVA_MIFE-0071741-51)	Q
OCP Memo	U.S. Food and Drug Administration, Office of Clinical Pharmacology Review Memorandum Addendum (January 20, 2012) (CORMIFE-T-00068918-20)	R

Short Citation*	Full Citation	Exhibit Number
Oosterhuis	J.K. Oosterhuis et al., "Life-threatening *Pneumocystis jiroveci* pneumonia following treatment of severe Cushing's syndrome," *Netherlands J. Med.*, 65(6):215-17 (2007) (CORMIFE-T-00011108-10)	S
Pivonello	R. Pivonello et al., "The Treatment of Cushing's Disease," *Endocrine Reviews*, 36(4):385-486 (2015) (TEVA_MIFE-0071863-964)	T
Teva Label	Teva Mifepristone Tablets Full Prescribing Information (TEVA_MIFE-0120842-61)	U
Viera	A.J. Viera & N. Wouk, "Potassium Disorders: Hypokalemia and Hyperkalemia," *Am. Family Physician*, 92(6):487-95 (2015)	V

* All Exhibits cited herein are referred to by their "Short Citation" and attached to the Declaration of Nicholas A. LoCastro submitted herewith.

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I. INTRODUCTION

In this Hatch-Waxman patent infringement case between Plaintiff Corcept Therapeutics, Inc. ("Corcept") and Defendant Teva Pharmaceuticals USA, Inc. ("Teva"), the last-to-expire patent-in-suit is U.S. Patent No. 10,195,214 ("the '214 Patent"). Recently, the Patent Trial and Appeal Board upheld the validity of the '214 Patent against Teva's Post-Grant Review challenge.[1] As a result of that ruling, Teva agrees that it is estopped, pursuant to 35 U.S.C. § 325(e)(2), from contesting the validity of the '214 Patent before this Court. Accordingly, infringement is the only issue remaining regarding the '214 Patent.

The '214 Patent claims methods of treating Cushing's syndrome and manifestations thereof by administering certain amounts of the drug mifepristone in combination with certain other drugs known to strongly inhibit the CYP3A family of enzymes (known as "strong CYP3A inhibitors"). The material facts that form the basis of Corcept's infringement claim are undisputed. Specifically, the infringement inquiry will be governed by Teva's proposed package insert, the content of which is not in question. Nor is it disputed that Teva's package insert instructs healthcare providers how to perform each step of each claim of the '214 Patent.

What Teva does dispute is whether the content of its package insert permits the Court to infer that it has the requisite intent to induce healthcare providers to practice the claimed methods. This is a legal issue, and a straightforward application of binding precedent indicates that Teva's position is meritless, and this case is ripe for summary adjudication. Specifically, the Federal Circuit has repeatedly held that the filer of an Abbreviated New Drug Application ("ANDA") has the requisite specific intent to induce infringement where its "proposed label itself recommends infringing acts." *Vanda Pharm. Inc. v. W.-Ward Pharm. Int'l Ltd.*, 887 F.3d

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[1] *See Teva Pharmaceuticals USA, Inc. v. Corcept Therapeutics, Inc.*, PGR2019-00048, Paper No. 51 (P.T.A.B. Nov. 18, 2020).

1117, 1133 (Fed. Cir. 2018). Here, it is undisputed that Teva's label includes instructions that plainly direct healthcare providers how to practice each step of each asserted claim. And because these instructions are ***the only*** dosing instructions for healthcare providers to follow in order to co-administer mifepristone with strong CYP3A inhibitors, the law is clear that the Court may infer intent from Teva's label. The Court can therefore decide on summary judgment, without the need for trial, that Teva will induce infringement of Claims 1-13 of the '214 Patent.

II. FACTUAL BACKGROUND

A. State of the Art Prior to the Claimed Inventions

1. Cushing's Syndrome is a Debilitating and Difficult-to-Treat Disorder

Cushing's syndrome is a "debilitating endocrine disorder" caused by elevated levels of the hormone cortisol, which are usually the result of tumors that afflict the pituitary or adrenal glands. Morgan at Abstract; Pivonello at 385-86. "The excess cortisol seen in Cushing's syndrome results in hypertension, hyperglycemia [high blood sugar], obesity, and a myriad of other problems." Morgan at 320. These myriad other problems include "a risk of life-threatening cardiovascular, infectious and metabolic complications." Guelho at 464. Excess cortisol (hypercortisolemia) can also have "major effects on the brain that can result in psychopathology and neurocognitive dysfunction." *Id*. As such, Cushing's syndrome is "associated with significant morbidity and mortality." Fleseriu 2013(a) at 1.

The first line treatment for patients with Cushing's syndrome is surgery to remove the tumors responsible for generating the excess cortisol. Morgan at 319. Many patients are not candidates for surgery, however, often because they are too sick to survive the procedure or have tumors that cannot be located or completely removed. These patients require pharmacological treatment. *See id*.

2. Korlym® (Mifepristone) Is a First-in-Class Glucocorticoid Receptor Antagonist

Corcept's commercial drug product is marketed under the brand name Korlym®. SMF at ¶ 1. The active ingredient in Korlym® is mifepristone. *Id.* at ¶ 2. Korlym® was approved by the FDA in 2012 as an orphan drug to control hyperglycemia in patients with Cushing's syndrome who are not surgical candidates or have not achieved remission from surgery.[2] *Id.* at ¶ 3. The use of Korlym® has been found to result in "rapid control of the systemic effects of cortisol excess in patients with [Cushing's syndrome]." Cuevas-Ramos at 6.

Mifepristone works through a mechanism of action that differs from other therapies for Cushing's syndrome. Specifically, rather than lowering elevated levels of cortisol, mifepristone blocks the receptors to which cortisol seeks to bind (known as glucocorticoid receptors), "thereby decreasing the physiologic effects of hypercortisolemia." Morgan at 323; Fleseriu 2013(b) at 314. Mifepristone's distinct mechanism of action renders it "rapidly effective in controlling hypercortisolism," which allows it to play a unique "role in the management of [Cushing's syndrome], especially when the presence of severe disease or concomitant conditions requires a rapid control of cortisol excess." Pivonello at 455. Korlym® is the first glucocorticoid receptor antagonist approved for the treatment of the manifestations of Cushing's syndrome. *Id.*

Although mifepristone has the ability to rapidly control hypercortisolism, the drug can be difficult to dose effectively. Since mifepristone does not lower circulating cortisol levels but instead blocks the action of cortisol by preventing its binding at receptor sites, it can be "***very difficult*** to dose titrate [mifepristone] and judge effectiveness." Dang at 1345 (emphasis added). The art, and in particular Korlym®'s original package insert, taught that mifepristone could be

[2] Hyperglycemia (high blood sugar) is common amongst patients with Cushing's syndrome and is caused by the elevated cortisol levels that characterize the disease. Fleseriu 2012 at 2046; Morgan at 320. If left untreated, hyperglycemia can become severe and lead to serious complications requiring emergency care, such as a diabetic coma. *See, e.g.*, Mayo Clinic.

dosed from 300 to 1200 mg per day for the treatment of Cushing's syndrome, *see* 2012 Korlym® Label, but also that many patients did not respond to lower doses within that range. In fact, in the Phase III clinical trial that led to FDA approval of the drug, the 300 mg dose was effective in only 13.3 percent of patients who ultimately responded to mifepristone treatment, while the remaining 86.7 percent of patients who responded only did so once their doses were increased to higher levels, such as 600 mg per day. Fleseriu 2012 at 2042.

Following administration, mifepristone is metabolized by the CYP3A enzyme. SMF at ¶ 4. Mifepristone is therefore characterized as a CYP3A substrate. *Id.* at ¶ 5.

3. Patients with Cushing's Syndrome Often Take Multiple Drugs

Patients with Cushing's syndrome generally experience "several comorbidities," and the "mortality associated" with Cushing's syndrome has been "demonstrated to be strongly dependent on … mainly cardiovascular disease and infectious diseases." Pivonello at 386-87. This susceptibility to infection "is a direct consequence of the immunosuppression induced by hypercortisolism." *Id.* at 392. The art states that "[t]he risk of an opportunistic infection in Cushing's syndrome [was known to be] related to the cortisol level" of the patient, and "opportunistic infection[s]" were most common in patients "with higher levels of cortisol overproduction." Oosterhuis at 216. Since approval, the Korlym® package insert has taught (and continues to teach) that "[p]atients with endogenous Cushing's syndrome are at risk for opportunistic infections such as *Pneumocystis jiroveci* pneumonia during Korlym treatment." 2012 Korlym® Label at 6; 2019 Korlym® Label at 6. As a result, "sepsis [caused by systemic infection] is one of the most common and severe causes of death [from Cushing's syndrome]." Pivonello at 392. Patients with Cushing's syndrome, therefore, may require treatment with anti-infectious agents, and certain anti-infectious agents—such as ketoconazole, itraconazole and clarithromycin—are well-known strong CYP3A inhibitors. SMF at ¶ 14. For example, one of

the "most frequently found pathogens" in patients with Cushing's syndrome is *Aspergillus fumigatus*, which is treated with itraconazole. Oosterhuis at 216; CDC; Itraconazole Label at 6.

Moreover, although mifepristone is effective in the management of Cushing's syndrome, at the time of invention, "no single drug ha[d] demonstrated complete efficacy in the treatment of [Cushing's syndrome]." Cuevas-Ramos at 6. As such, one strategy was "to combine drugs with additive, synergistic, and/or complementary mechanisms of action." *Id.*

Ketoconazole, an antifungal that had been approved at the time of the invention to treat certain systemic infections, was also often prescribed to treat Cushing's syndrome due to its ability to inhibit cortisol synthesis. In fact, prior to the approval of Korlym®, ketoconazole was "the most frequently used agent in the treatment of Cushing's syndrome." Dang at 1341. The art further disclosed that, "[b]ecause ketoconazole is readily available and has a mechanism of action distinct from mifepristone, the combination of mifepristone with ketoconazole is a logical choice and may have added benefit for the treatment of Cushing's syndrome." Morgan at 326. The FDA, too, recognized upon approving Korlym® that there was a "high potential [for ketoconazole's] concomitant use with mifepristone." OCP Memo at 1. Even Teva has argued that "it ha[s] been known for years that ketoconazole could treat Cushing's, and moreover that clinicians might need to use combination therapy involving mifepristone and ketoconazole to treat patients who have the disease." *Teva Pharmaceuticals USA, Inc. v. Corcept Therapeutics Inc.*, PGR2019-00048, Paper 1 at 11 (P.T.A.B. May 7, 2019). Moreover, as discussed above, it was well-known in the art that ketoconazole strongly inhibits CYP3A. SMF at ¶ 14.

B. The '214 Patent Claims Methods of Concomitantly Administering 600 mg Mifepristone with a Strong CYP3A Inhibitor

Prior to the invention of the methods claimed in the '214 Patent, the art stated that the co-administration of Korlym® and strong CYP3A inhibitors "could substantially increase the

concentration of mifepristone in the blood," and that "increased exposure to mifepristone [was] associated with serious risks for severe hypokalemia and adrenal insufficiency." *See* 2012 Korlym® Label at 6; FDA Approval Letter at 3. Both adrenal insufficiency and hypokalemia are potentially life-threatening conditions. *See* Charmandari at Abstract (describing adrenal insufficiency as "a life-threatening disorder"); Viera at Abstract (explaining that "when severe," hypokalemia "can lead to life-threatening cardiac conduction disturbances and neuromuscular dysfunction."). As such, the 2012 Korlym® Label stated that "Korlym should be used with extreme caution in patients taking ketoconazole and other strong inhibitors of CYP3A … and in such cases the dose should be limited to 300 mg per day." *See* 2012 Korlym® Label at 6.

After Korlym® had obtained FDA approval in 2012, Corcept sponsored several clinical trials designed to further study the effects of co-administering mifepristone with ketoconazole and other strong CYP3A inhibitors. SMF at ¶¶ 6-8. Based upon these clinical trials, Corcept discovered that it is actually safe to co-administer 600 mg of mifepristone—double the previously taught "limit"—in combination with a strong CYP3A inhibitor to treat Cushing's syndrome and its manifestations.

At the conclusion of the recent Post Grant Review proceeding initiated by Teva regarding the '214 Patent, the Patent Trial and Appeal Board found that prior to Corcept's drug-interaction clinical trials, persons skilled in the art would not "reasonably have expected coadministration of more than 300 mg of mifepristone with a strong CYP3A inhibitor to be safe for the treatment of Cushing's syndrome or related symptoms in patients." *See Teva Pharmaceuticals USA, Inc. v. Corcept Therapeutics Inc.*, PGR2019-00048, Paper 51 at 49 (P.T.A.B. Nov. 18, 2020). The Korlym® package insert was subsequently updated to reflect Corcept's discovery. *Compare, e.g.*, 2012 Korlym® Label at Table 3 *with* 2019 Korlym® Label at Table 3.

The '214 Patent claims certain methods of treating Cushing's syndrome and its manifestations wherein patients taking once-daily doses of 1200 mg or 900 mg mifepristone have their dose reduced to 600 mg in order to co-administer a strong CYP3A inhibitor selected from a group consisting of ketoconazole, itraconazole, clarithromycin, and other strong inhibitors. SMF at ¶ 9.

The independent claims of the '214 Patent (claims 1, 5, and 10) are identical except claim 1 recites a method of "treating Cushing's syndrome," claim 5 recites a method of "treating symptoms associated with elevated cortisol levels," and claim 10 recites a method of "controlling hyperglycemia secondary to hypercortisolism." *Id.* at ¶ 10. The dependent claims recite the specific strong CYP3A inhibitor to be dosed in combination with mifepristone. *Id.* at ¶¶ 12-13. Claim 10 is representative and presented below:

> **10**. A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:
>
> reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,
>
> administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,
>
> wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

Id. at ¶ 11.

C. Teva Seeks FDA Approval to Market a Generic Mifepristone Product with Instructions that Read on the Claims of the '214 Patent

Teva has filed ANDA No. 211436 with the FDA, through which it seeks to market a generic version of Korlym®. *Id.* at ¶ 15. Teva's labeling (or package insert) for its generic

mifepristone product reflects how Teva intends for physicians to use its product. *Id.* at ¶¶ 16-18.

[redacted] *Id.* at ¶ 19 [redacted]. Teva's package insert is identical in all material respects to the current Korlym® package insert. *Id.* at ¶ 20.

The content of Teva's package insert is undisputed. The Indications and Usage section of Teva's package insert states that Teva's mifepristone product is "indicated to control hyperglycemia secondary to hypercortisolism in [certain] adult patients with endogenous Cushing's syndrome." *Id.* at ¶ 21. The Dosage and Administration section of Teva's package insert states that the "recommended starting dose is 300 mg orally once daily," and that the daily dose "may be increased in 300 mg increments … to a maximum of 1,200 mg once daily." *Id.* at ¶ 22.

The Dosage and Administration section also includes a subsection titled "Concomitant Administration with CYP3A Inhibitors." *Id.* at ¶ 23. This subsection of the package insert provides "dose adjustment" steps for physicians to follow for adding a strong CYP3A inhibitor to the treatment regimen of "patients already being treated with mifepristone tablets." *Id.* at ¶ 24. The instructions in Teva's package insert for adding a strong CYP3A inhibitor to the treatment regimen of a patient receiving an original mifepristone dose of 900 mg require that the physician "reduce dose to 600 mg" before adding the strong CYP3A inhibitor. *Id.* at ¶¶ 25-27. This specific dose adjustment instruction is the only dosing option presented in the label "when [a] strong CYP3A inhibitor is added" to the treatment regimen of a patient receiving an original mifepristone dose of 900 mg. *Id.*

The Clinical Pharmacology section of Teva's package insert contains a table showing data derived from the "in vivo assessment of drug interactions." *Id.* at ¶ 30. The data are derived from two clinical studies (in human volunteers) in which mifepristone was co-administered with strong CYP3A inhibitors. In the first study, 600 mg of mifepristone was co-administered with ketoconazole. *Id.* at ¶ 31. In the second, 900 mg of mifepristone was co-administered with itraconazole. *Id*. Teva's package insert includes data regarding the increase in mifepristone blood serum concentrations as a result of co-administration with the strong CYP3A inhibitors, and states that a "dose adjustment [is] required" in order to co-administer mifepristone with either of ketoconazole or itraconazole. *Id.* at ¶ 32.

As explained more fully below, the language and data in the Dosage and Administration and Clinical Pharmacology sections of Teva's package insert plainly instruct a physician to perform each and every step of the methods claimed in the '214 Patent. And because Teva: (1) intends for physicians to use its ANDA Product in accordance with its package insert, and (2) intends to market its ANDA Product with a package insert that plainly instructs doctors to engage in an infringing use, well-settled precedent makes clear that, as a matter of law, Teva has the requisite intent to induce infringement. The Court should therefore grant summary judgment.

III. LEGAL STANDARD

A. Summary Judgment

Summary judgment shall be granted when "the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). A fact is not "material" unless proof of its existence or non-existence would affect disposition of the case under applicable law. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). An issue of material fact is not "genuine" unless the evidence offered is such that a reasonable fact finder might return a verdict for the non-movant. *Id*. To succeed, the party

seeking summary judgment need only show that "there is an absence of evidence to support the nonmoving party's case." *Celotex Corp. v. Catrett*, 477 U.S. 317, 325 (1986). To survive summary judgment, the non-moving party must then demonstrate that a fact finder could return a verdict in its favor. *Anderson*, 477 U.S. at 249. The non-moving party must present "specific facts" to support its case and "cannot rely on unsupported assertions, bare allegations, or speculation." *Schering Corp. v. Mylan Pharm., Inc.*, No. 09-6383, 2011 WL 3736503, at *1 (D.N.J. Aug. 22, 2011). "Only disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment. Factual disputes that are irrelevant or unnecessary will not be counted." *Anderson*, 477 U.S. at 248.

B. Induced Infringement of a Method of Treatment Patent Under the Hatch-Waxman Act

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). The Federal Circuit has held that "inducement can be found where there is evidence of active steps taken to encourage direct infringement, which can in turn be found in advertising an infringing use or instructing how to engage in an infringing use." *Vanda Pharm.*, 887 F.3d at 1129. The Federal Circuit has found the "requisite specific intent to induce infringement [where the generic drug company] included instructions in its proposed label that will cause at least some users to infringe the asserted method claims." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010); *see also Vanda Pharm.*, 877 F.3d at 1133 (finding intent to induce where "the proposed label itself recommends infringing acts.").

In Hatch-Waxman cases where the proposed ANDA product label contains "instructions [that] are unambiguous on their face" and teach healthcare providers to practice an infringing use, those instructions "encourage or recommend infringement." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1368-69 (Fed. Cir. 2017). To that end, both the

Federal Circuit and courts within this District have routinely found that proposed ANDA product labels evidence the requisite intent to induce where—like here—they plainly instruct doctors to engage in an infringing use. *See, e.g.*, *Braintree Labs. v. Breckenridge Pharm., Inc.*, 688 F. App'x 905, 910 (Fed. Cir. 2017) ("Because Breckenridge's ANDA label 'instruct[s] how to engage in an infringing use, [it] show[s] an affirmative intent that the product be used to infringe.'" (alteration in original)); *Sanofi v. Watson Labs Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017) ("The content of the label in this case permits the inference of specific intent to encourage the infringing use."); *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 352 F. Supp. 3d 352, 397 (D.N.J. 2018) ("In the context of patent infringement litigation involving pharmaceuticals, 'the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent.'" (citation omitted)). There is no question that "[i]n the Hatch–Waxman context, statements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement for purposes of inducement to infringe under 35 U.S.C. § 271(b)." *Bone Care Int'l, LLC. v. Roxane Labs., Inc.*, No. 09-285, 2012 WL 2126896, at *9 (D. Del. June 11, 2012) (citation and quotations omitted).

IV. ARGUMENT

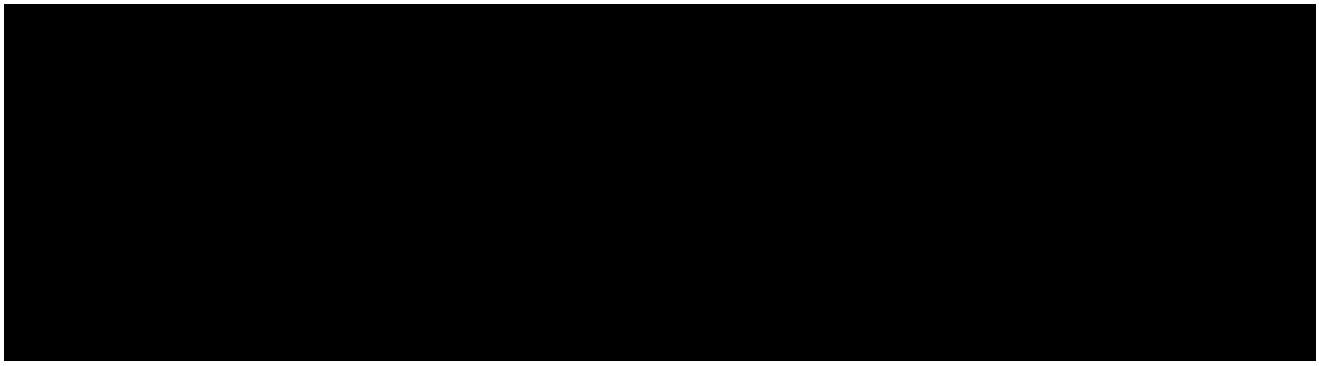
A. The Undisputed Facts Demonstrate that Teva's Package Insert Plainly Instructs Healthcare Providers to Engage in an Infringing Use

There are four elements to Claim 10 of the '214 Patent.[3] For the reasons below, the undisputed facts demonstrate that healthcare providers using Teva's ANDA Product according to its labeling are instructed to practice each of these four elements.

[3] As explained above, Claim 10 is representative of the other asserted independent claims. *See supra* at § II(B).

1. It is Undisputed that Teva's Package Insert Instructs "A method of controlling hyperglycemia secondary to hypercortisolism in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone"

The Dosage and Administration section of Teva's package insert instructs healthcare providers to use Teva's ANDA product to control hyperglycemia secondary to hypercortisolism in patients who are taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone. Teva's ANDA product is specifically indicated "to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome." SMF at ¶ 21. Further, Teva's package insert instructs healthcare providers that the manifestations of Cushing's syndrome, such as hyperglycemia secondary to hypercortisolism, may be controlled by administering 1200 mg or 900 mg of mifepristone:



SMF at ¶ 22 (highlighting added).

2. It is Undisputed that Teva's Package Insert Instructs "reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone"

The Dosage and Administration section of Teva's package insert provides unequivocal instructions to healthcare providers to ensure safety when co-administering mifepristone and strong CYP3A inhibitors that require reducing the mifepristone dose to 600 mg per day. As shown below, for a patient who is receiving a "[c]urrent dose" of 900 mg mifepristone and a

strong CYP3A inhibitor is added to the patient's treatment regimen, Table 1 of Teva's package insert instructs the prescriber to reduce the 900 mg mifepristone dose to 600 mg:

SMF at ¶¶ 25-27 (highlighting added).

When adding a strong CYP3A inhibitor to the treatment regimen of a patient already receiving mifepristone, the only dose titration instructions in Teva's label are those provided in Table 1. Teva's labeling does not provide any other options or instructions. In other words, when a physician administers a strong CYP3A inhibitor to a patient who was already taking a 900 mg dose of Teva's ANDA product, the ***only*** course of action encouraged and taught by Teva's label is to practice the claim element by reducing the mifepristone dose to 600 mg.

Moreover, the Clinical Pharmacology section of Teva's package insert contains actual clinical data demonstrating the safety of co-administering 600 mg mifepristone with a strong CYP3A inhibitor. Specifically, Teva's label discloses (Corcept's) *in vivo* data showing that the co-administration of 600 mg mifepristone with a strong CYP3A inhibitor will not cause mifepristone blood serum levels to rise to unsafe levels:

SMF at ¶¶ 31-32.[4] Table 3 of Teva's package insert further states that the "[d]ose adjustment" is "**required**" in order to add a strong CYP3A inhibitor to the treatment regimen of a patient already receiving high doses of mifepristone. *Id.*

3. It is Undisputed that Teva's Package Insert Instructs "administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient"

There is no dispute that the Dosage and Administration section of Teva's package insert instructs healthcare providers that upon reducing the original once-daily dose of 900 mg per day, the adjusted once-daily dose of 600 mg is administered to the patient in combination with a strong CYP3A inhibitor. More specifically, under a heading titled "Concomitant Administration with CYP3A Inhibitors," Section 2.5 of Teva's package insert states that "when necessary," mifepristone "should be used in combination with strong CYP3A inhibitors." SMF at ¶¶ 28-29. The package insert then proceeds to provide the specific mifepristone dosage adjustment down to 600 mg in Table 1, which is entitled "Dose adjustment of mifepristone when strong CYP3A inhibitor is added." *Id.* at ¶¶ 27-29.

[4] Several rows of Table 3 have been omitted here for ease of reading.

4. It is Undisputed that Teva's Package Insert Instructs selecting the strong CYP3A inhibitor "from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole"

There is also no dispute that Teva's package insert instructs healthcare providers that the strong CYP3A inhibitors that should be administered in combination with the adjusted once-daily dose of mifepristone includes most of the compounds identified in the claim. Teva's package insert specifically calls out the majority of the claimed CYP3A inhibitors, including: ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, nelfinavir, indinavir, conivaptan, lopinavir, posaconazole, saquinavir, and voriconazole. SMF at ¶ 28. Moreover, there are dependent claims specifically directed to the co-administration of each of ketoconazole, itraconazole, and clarithromycin with 600 mg of mifepristone. *See* SMF at ¶¶ 12-13 (citing '214 Patent at Claims 2-4, 5-9, and 11-13).

Accordingly, as illustrated in the claim chart below, there is no material dispute that the package insert for Teva's ANDA product instructs healthcare providers to perform all of the elements of an infringing use of the '214 Patent when they add a strong CYP3A inhibitor to the treatment regimen of a patient receiving an original once-daily dose of 900 mg mifepristone:

Claim Element	Teva's Labeling
A method of controlling hyperglycemia secondary to hypercortisolism in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:	Teva's ANDA product is indicated "to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome." SMF at ¶ 21. Teva's package insert instructs healthcare providers that the manifestations of Cushing's syndrome, such as hyperglycemia secondary to hypercortisolism, may be controlled by administering 1200 mg or 900 mg of mifepristone. SMF at ¶ 22.

Claim Element	Teva's Labeling
reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,	Table 1 instructs to "reduce dose to 600 mg" mifepristone "when [a] strong CYP3A inhibitor is added." SMF at ¶ 27. Table 3 states that a "[d]ose adjustment" is "required" in such circumstances. SMF at ¶ 32.
administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,	Section 2.5 states that "when necessary," the reduced mifepristone dose should be "used in combination with strong CYP3A inhibitors." SMF at ¶¶ 28-29.
wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.	Section 2.5 of Teva's package insert instructs that the "strong inhibitors of CYP3A" that may be "used in combination" with mifepristone "when necessary" include "ketoconazole, … itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, … clarithromycin, conivaptan, lopinavir/ritonavir, … posaconazole, saquinavir, … or voriconazole." SMF at ¶ 28.

B. The Court May Therefore Conclude as a Matter of Law that Teva Has the Requisite Intent to Induce Infringement

Teva does not dispute that it intends for physicians to follow the instructions set forth in its package insert. [redacted]

As set forth above, there can be no dispute that Teva's label presents a series of instructions for healthcare providers to follow when co-administering mifepristone with strong CYP3A inhibitors. Specifically, when adding a strong CYP3A inhibitor to the treatment regimen of a patient already receiving a 900 mg mifepristone dose, Teva's label unambiguously instructs healthcare providers to reduce the mifepristone dose to 600 mg for co-administration. That dosing regimen reads directly on the asserted claims of the '214 Patent. Teva's label does

not provide any conflicting or alternate dosing regimens for healthcare providers to choose from. The Court therefore can infer, as a matter of law and consistent with well-established precedent, that the clear instructions provided in Teva's label will induce infringement of the claimed methods. *See Vanda Pharm.*, 887 F.3d at 1133 (defendant had requisite intent to induce where its "proposed label itself recommends infringing acts"); *see also, e.g.*, *Braintree Labs.*, 688 F. App'x at 910 ("Because Breckenridge's ANDA label 'instruct[s] how to engage in an infringing use, [it] show[s] an affirmative intent that the product be used to infringe.'" (alteration in original)); *Sanofi*, 875 F.3d at 646 ("The content of the label in this case permits the inference of specific intent to encourage the infringing use."); *BTG Int'l Ltd.*, 352 F. Supp. 3d at 397 ("In the context of patent infringement litigation involving pharmaceuticals, 'the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent.'" (citation omitted)). Accordingly, as a matter of law, Teva intends to induce infringement of the claims of the '214 Patent. Summary judgment should be granted.

Expert testimony is not required to determine that Teva infringes the '214 Patent. As set forth above, there is a readily apparent correlation between the undisputed content of Teva's package insert and the claims of the '214 Patent. An expert need not testify whether the instructions in the package insert read upon the claims when it is clear to a layperson that the instructions in the package insert and the steps of the claim are the same. For instance, another court in this District granted summary judgment of induced infringement in similar circumstances. In *Hoffmann-La Roche Inc. v. Apotex Inc.*, there was "no genuine dispute that the proposed product labels direct patients to take actions which constitute infringement of [the asserted claims]." No. 07-4417, 2010 WL 3522786, at *3 (D.N.J. Sept. 2, 2010) (Chesler, J.). The defendants in *Hoffman* attempted to argue that they nonetheless did not intend to induce

infringement because patients could choose instead to use the products for "substantial non-infringing uses." *Id.* The court rejected that argument as a matter of law, explaining that the defendants "are expressly instructing others to perform a method which infringes a method patent. The fact that they may, in addition, be instructing others to do things which do not infringe has no bearing on the inference of specific intent to induce infringement." *Id.* at *4. The court therefore found summary judgment appropriate, because where "the evidence unequivocally demonstrates that Defendants intend that their purchasers follow the [infringing] package insert instructions, [they] therefore have the requisite specific intent to induce infringement." *Id.* at *5.

The same conclusion is warranted here. It is undisputed that Teva's package insert provides step-by-step instructions that direct healthcare providers to practice each element of the methods claimed in the '214 Patent when they co-administer mifepristone with strong CYP3A inhibitors. It is therefore immaterial that Teva's ANDA product can also be put to other uses; the fact that the package insert plainly instructs healthcare providers to engage in the infringing use demonstrates as a matter of law that Teva has the requisite intent to induce infringement. The Federal Circuit has made clear that where the proposed ANDA product label contains "instructions [that] are unambiguous on their face" and teach healthcare providers to practice an infringing use, those instructions "encourage or recommend infringement." *Eli Lilly & Co.*, 845 F.3d at 1368-69. Accordingly, Corcept's motion for summary judgment should be granted.

C. Teva's Non-Infringement Defense Is Without Merit

In opposing Corcept's request for leave to file the instant motion, Teva took the position that the Federal Circuit's split-panel decision in *HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019), "demonstrates that Teva cannot be held liable for induced infringement based on [its proposed] label language." *See* February Letter. Teva went

so far as to claim that *HZNP* is "fatal to Corcept's infringement case." *Id.* Teva is wrong. *HZNP* is readily distinguishable and is not "fatal" to the straightforward and well-supported infringement case Corcept has set forth.

In *HZNP*, the patented method comprised three steps: (1) apply a topical medicinal formulation; (2) wait for the area to dry; and then (3) apply sunscreen, bug spray, or a second topical medication. *See* 940 F.3d at 702. The Federal Circuit held that the proposed generic label would not induce infringement where it did not match the patented claims, including that the label: (1) "only require[d] the first step of th[e claimed] method" and (2) was "broader than step three of [the] claimed method … beyond warning the user about waiting for the treated area to be completely dry before covering it with sunscreen, bug spray, or another topical medication, [the proposed] label also warns about clothing, cosmetics, lotion, water, moisturizer, and other substances." *Id.*

Teva has attempted to analogize *HZNP* to this case, arguing that it will not induce infringement because its own proposed label "does not require subsequent [administration of a strong CYP3A inhibitor]." February Letter (alteration original). In other words, Teva reads the *HZNP* case to stand for the proposition that inducement cannot be found where the instructions in the proposed package insert do not "require" healthcare providers to perform the patented method. Teva's reliance on *HZNP* is flawed both legally and factually.

1. *HZNP* Did Not Change the Law of Induced Infringement

As an initial matter, Teva's interpretation of *HZNP*, taken to its logical endpoint, would imply that a proposed generic drug label could never evidence the requisite intent to induce infringement. While a package insert provides up-to-date information from the drug manufacturer that healthcare providers can use to guide their prescribing practices, no package insert ever ***requires*** a healthcare provider to administer any given drug. *See, e.g.*, *Amarin*

Pharma, Inc. v. U.S. Food & Drug Admin., 119 F. Supp. 3d 196, 200 (S.D.N.Y. 2015) (explaining that "the FDA does not regulate doctors.").

The law of induced infringement recognizes this reality and does not demand a showing that the proposed generic label ***requires*** that the healthcare provider administer any particular drug in accordance with a patented method. Instead, the question is whether the label ***encourages or instructs*** a method of use that overlaps with the patented use. *See, e.g.*, *Vanda Pharm.*, 887 F.3d at 1133; *Braintree Labs.*, 688 F. App'x at 910; *Eli Lilly & Co.*, 845 F.3d at 1368-69. As the Federal Circuit has noted, it is immaterial that "not every practitioner will prescribe an infringing dose." *Vanda Pharm.*, 887 F.3d at 1132. Under the Hatch-Waxman framework, seeking FDA approval for a package insert that "instructs users to perform the patented method is sufficient to provide evidence of [Teva's] affirmative intent to induce infringement." *Id.* (citation and internal quotations omitted). Accordingly, Teva's interpretation of the *HZNP* holding is contrary to settled Federal Circuit precedent.[5]

Forest Labs. Holdings Ltd. v. Mylan Inc. is also instructive. There, the generic drug company defendants argued that their proposed label did not evidence an intent to induce infringement of patents covering improved methods of drug dosing because their label stated that the proposed generic drugs "***may*** be titrated according to the [claimed dosing] schedule," but such titration was not required. 206 F. Supp. 3d 957, 976 (D. Del. 2016) (emphasis original). The court rejected the argument that the labels had to ***require*** healthcare providers to administer the drug at issue in accordance with the claimed method, and instead explained that "[t]he crux

[5] Nor could *HZNP* have overturned the prior Federal Circuit precedent cited herein: "panels do not have the authority to overrule prior precedential panel decisions unless the en banc court or the Supreme Court overturns the prior decision." *Diamond Coating Techs., LLC v. Hyundai Motor Am.*, 823 F.3d 615, 621 (Fed. Cir. 2016) (citing *Deckers Corp. v. United States*, 752 F.3d 949, 965 (Fed. Cir. 2014)).

of induced infringement is that defendants have included the exact titration schedule as claimed in the [asserted patents] and have made no effort to remove the titration schedule from the labels or submit a Paragraph III certification and wait for the asserted patents to expire." *Id.* at 977-78. Thus, the court concluded that the generic company's label induced infringement of the patented method.

The same is true here. Teva seeks FDA approval of a package insert that contains dose titration steps that directly overlap with the claimed method. [redacted]. It has done neither of those things. The Court may therefore find Teva has the requisite intent to induce. *Forest*, 206 F. Supp. 3d at 977-78.

Moreover, even if Teva's reading of the *HZNP* case were correct—which, as set forth above, it is not—the Court should still find Teva has the requisite intent to induce infringement. It is undisputed that Teva's package insert instructs healthcare providers to co-administer mifepristone with strong CYP3A inhibitors "when necessary," and that Teva's package insert instructs ***one and only one*** course of action when adding a strong CYP3A inhibitor to the treatment regimen of a patient already receiving a 900 mg mifepristone dose: practice the claim and reduce the mifepristone dose to 600 mg. It is further undisputed that the Clinical Pharmacology section of Teva's package insert instructs healthcare providers that the claimed dosage adjustments ***are*** "required" in instances when mifepristone is co-administered with strong CYP3A inhibitors, and provides clinical data establishing that co-administration of the adjusted 600 mg dose is safe. *Supra* at § IV(A)(2); SMF at ¶¶ 31-32. Thus, Teva seeks FDA approval for a package insert that not only instructs healthcare providers how to perform each step of the

claimed methods, but also instructs those providers that such dosage adjustments are in fact "required" and includes human clinical trial data confirming that the claimed methods are safe. The Court can infer that the inclusion of these "required" instructions and supporting safety data in Teva's label will encourage at least some doctors to practice the claimed method, and therefore that Teva has the requisite intent to induce infringement. *See, e.g.*, *Amarin Pharma, Inc. v. Hikma Pharm. USA Inc.*, 449 F. Supp. 3d 967, 1000 (D. Nev.), *aff'd*, 819 F. App'x 932 (Fed. Cir. 2020) (finding "explicit textual support for Plaintiffs' inducement theory in the Clinical Studies section of the labelling for all Asserted Claims—that a doctor would understand to suggest she should prescribe the drugs in an infringing way.").

2. *HZNP* Is Also Readily Distinguishable on Its Facts

The facts of this case are also very different than what the Federal Circuit addressed in *HZNP*. As explained above, in *HZNP*, the patented method comprised three steps: (1) apply a topical medicinal formulation; (2) wait for the area to dry; and then (3) apply sunscreen, bug spray, or a second topical medication. *See* 940 F.3d at 702. The proposed generic drug label, however, only instructed patients to perform the first step. The label also warned patients to wait "for the treated area to be completely dry" before covering it with anything else, such as clothing, cosmetics, lotion, water, moisturizer, sunscreen, bug spray, or another topical medication. *See id.* But nothing in the label actually encouraged or required patients to cover the affected area with anything else, much less the specific ointments required by the claims. The Federal Circuit held that the label did not encourage infringement of the claimed three-step method, because it was entirely up to the patient's discretion whether to ever perform the third step; i.e., to apply sunscreen or bug spray after applying their topical medicine. *Id.* Thus, there was no inducement in *HZNP* because a generalized *warning* to wait for one cream to dry before applying another would not necessarily encourage anyone to ever apply the second cream,

especially where adding a second cream like sunscreen or bug spray had nothing to do with treating the underlying condition or its co-morbidities.

This case is different. The '214 Patent claims *methods of treating* Cushing's syndrome and its manifestations by co-administering mifepristone with strong CYP3A inhibitors. As set forth above, Teva's package insert contains specific dose titration instructions that encourage healthcare providers to practice each and every step of those *methods of treatment*. This case does not concern a warning about waiting for one ointment to dry before applying another, where the consequences of not waiting could include getting a sunburn or a bug bite; it instead concerns a method of treating the manifestations of a serious endocrine disorder by combining prescription drugs at specific dosages where the wrong dose could prove fatal.

Indeed, unlike *HZNP*, the dose titration instructions in Teva's package insert at issue in this case provide specific prescribing information directed to healthcare providers, not a generalized warning to patients. Patients do not have the discretion to choose how their mifepristone doses are adjusted or whether they need to concomitantly take strong CYP3A inhibitors in the same way that patients have discretion to choose whether to apply over-the-counter items like sunscreen or bug-spray. [redacted] Teva's package insert, which provides dosing instructions for co-administering mifepristone with other prescription medications, is a document made for medical professionals. SMF at ¶ 17 [redacted]. Thus, the relevant question here is whether healthcare providers would be encouraged to follow the dose titration steps in the label when co-administering mifepristone with a strong CYP3A inhibitor—not whether a patient would be encouraged to apply one topical ointment after another (as in *HZNP*). *See also Amarin Pharma v. W.-Ward Pharm. Int'l Ltd.*, 407 F. Supp. 3d 1103, 1112 n.4 (D. Nev. 2019) (distinguishing *HZNP* and explaining the

question of how and whether a "doctor would look at the clinical studies portion of the labelling because of that doctor's medical training and experience would not apply in the situation addressed in *HZNP Medicines*, where the court was considering whether a patient would infringe."). Teva's package insert provides one and only one set of instructions (that overlap with the claimed methods) in circumstances where it is "necessary" to co-administer mifepristone with a strong CYP3A inhibitor, states that healthcare providers are "required" to follow those instructions in order to safely co-administer these drugs, and contains data from clinical trials in human volunteers indicating that the concomitant dosing method is safe. *See* SMF at ¶¶ 29, 31-32. The Court can therefore infer that the inclusion of these instructions and safety data in Teva's label will encourage at least some doctors to practice the claimed method. *See Forest*, 206 F. Supp. 3d at 976-78; *see also Amarin Pharma*, 449 F. Supp. 3d at 1000; *Vanda Pharm.*, 887 F.3d at 1133; *Braintree Labs.*, 688 F. App'x at 910; *Eli Lilly & Co.*, 845 F.3d at 1368-69.

Accordingly, the Court can determine as a matter of law that Teva will induce infringement of the claims of the '214 Patent.

V. CONCLUSION

For the foregoing reasons, Corcept respectfully requests that the Court enter summary judgment of infringement of claims 1-13 of the '214 Patent.

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Respectfully submitted,

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